REMARKS/ARGUMENTS

Claims 1-9, 13-32, directed to the following species: 1) BCG and interferon gamma, or LPS, TNF-alpha as maturing agent, and 2) CD86 or CD80 co-stimulatory molecule have been examined in the instant application. The Examiner has rejoined the claims directed to the species of dendritic cells obtained from skin, spleen, bone marrow, thymus, lymph nodes; the claims directed to umbilical cord blood with the species of dendritic cells obtained from peripheral blood; claims directed to the species LPS and TNF-alpha with the species BCG and interferon gamma, and claims directed to the species CD80 with the species CD86. The Examiner has reconsider the previous request for restriction and rejoined each of these species because the species have been found in the art.

The Examiner has decided not to rejoin species directed to: 1) a maturation agent, which is an imidazoquinoline compound, a synthetic double stranded polyribonucleotide, a agonist of a Toll-like receptor (TLR), a sequence of nucleic acids containing unmethylated CpG motifs known to induce the maturation of DC, or any combination thereof, and 2) co-stimulatory agent CD54. These species have been withdrawn from consideration by the Examiner as being drawn to non-elected species.

Applicant appreciates the Examiner's reconsidered the restriction requirement in the present application and that certain species have been rejoined for continued prosecution. Applicant maintains that all of the species should be considered together in the present application and respectfully request the Examiner further reconsider the need for restriction. In the present response all remarks are directed to the currently elected species although certain claims have not been amended to cancel the non-elected subject matter. Should the generic claims be found allowable, Applicant respectfully requests rejoinder of a reasonable number of non-elected species as set forth in M.P.E.P. § 821.04.

Applicant notes that the prior rejections under 35 U.S.C. § 112, first paragraph have been withdrawn.

Rejections Under 35 USC § 102:

Claims 1, 2, and 5 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Labeur *et al.*, *J. Immunol.* 162:168-175, 1999, for reasons already of record in the paper of October 18, 2007. The Examiner has summarized Applicant's prior response as asserting that Labeur *et al.* fail to teach that the partially matured dendritic cells have not been exposed to tumor. In addition, the prior response has been summarized as asserting that the dendritic cells taught by Labeur *et al.* are contacted with antigen before administration to an individual to be treated.

The prior response has not been found persuasive because the Examiner believes that it argues limitations not in the claims. In particular, the Examiner does not believe that the claims limit that the administered, partially matured dendritic cells have not been exposed to tumor and that the ability to take up and process antigen by the dendritic cells is *in vivo*. Labeur *et al.* is asserted by the Examiner to certainly teach that dendritic cells can take up and process antigen. Said dendritic cells are believed by the Examiner to be able to induce an anti-tumor response subsequent to administration to a cancer patient.

Applicant strongly disagrees with the allegations and assertions of the Examiner, but to further expedite prosecution claim 1 has been amended to recite "[a] method for producing an anti-tumor immune response comprising administration to an individual with a cancerous tumor a cell population comprising partially matured dendritic cells that have been partially matured *in vitro*, wherein the partially matured dendritic cells take up and process antigen *in vivo* and are enabled to induce an anti-tumor immune response subsequent to administration to the individual". Such amendment is believed to point out with greater particularity the method comprises administering an individual partially mature dendritic cells that have been induced to

mature *in vitro* and that contact with antigen occurs *in vivo* subsequent to administration. Labeur *et al.* do not disclose or suggest such a method.

Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 1, 2 and 5 as being anticipated by Labeur *et al.* in view of the amendments and remarks above.

Rejections Under 35 USC § 103:

Claims 2 through 4 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Labeur *et at. J. Immunol.* 162:168-175, 1999, *supra*, in view of Murphy *et al.* (US 5,788,963), for reasons already of record in paper of October 18, 2007. Applicant's prior response has been summarized by the Examiner as asserting that Labeur *et al.* fail to teach that the partially matured dendritic cells have not been exposed to tumor. The Examiner further alleges that Applicant's prior response asserts that the dendritic cells taught by Labeur *et al.* are contacted with antigen before administration to an individual to be treated. Further, the Examiner alleges that the prior response asserts that Murphy *et al.* may teach various source for dendritic cell precursors, and a method for *in vitro* contacting the dendritic cells with a prostate cancer antigen, but that there is no teaching or suggestion for administrating partially matured dendritic cells that have not been exposed to tumor antigen.

Applicant's prior response is not considered to be persuasive because the Examiner believes that the response argues a limitation not in the claims. In particular, the Examiner does not believe that the claims limit the administered composition to partially matured dendritic cells that have not been exposed to tumor and that the ability to take up and process antigen by the dendritic cells is *in vivo*. The dendritic cells taught by Labeur *et al* has asserted by the Examiner to certainly take up and process antigen. In addition, the Examiner has that the dendritic cells are able to induce an anti-tumor response subsequent to administration to a cancer patient.

Applicant strongly disagrees with the allegations and assertions of the Examiner, but to further expedite prosecution claim 1 upon which claims 2 through 4 depend has been amended to recite "[a] method for producing an anti-tumor immune response comprising administration to an individual with a cancerous tumor a cell population comprising partially matured dendritic cells that have been partially matured *in vitro*, wherein the partially matured dendritic cells take up and process antigen *in vivo* and are enabled to induce an anti-tumor immune response subsequent to administration to the individual". Such amendment is believed to point out with greater particularity the method comprises administering an individual partially mature dendritic cells that have been induced to mature *in vitro* and that contact with antigen occurs *in vivo* subsequent to administration. Labeur *et al.* do not disclose or suggest such a method and Murphy *et al.* do not teach or suggest the element missing from Labeur *et al.*

Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 2 through 4 as being unpatentable over Labeur *et al.* in view of Murphy *et al.* in light of the amendments and remarks above.

Claims 6 through 9 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Labeur *et al. J. Immunol.* 162:168-175, 1999 (*supra*) in view of US 20050059151 (Bosch *et al.*), and Chakraborty *et al. Clin. Immunol.* 94:88-98, 2000), for reasons already of record. The Examiner has summarized Applicant's prior response as asserting that Labeur *et al.* fail to teach that the partially matured dendritic cells have not been exposed to tumor. In addition, the Examiner has asserted that the response argues that the dendritic cells taught by Labeur *et al.* are contacted with antigen before administration to an individual to be treated. Further, the Examiner has asserted that the response alleges that there is no teaching or suggestion in Bosch *et al.* or Chakraborty *et al.* for administrating partially matured dendritic cells that have not been exposed to tumor antigen.

Applicant's prior response has been considered but is not found to be persuasive for the following reason:

The response argues limitation not in the claims. The claims do not limit that the administered, partially matured dendritic cells have not been exposed to tumor and that the ability to take up and process antigen by the dendritic cells is *in vivo*. The dendritic cells taught by Labeur et at certainly can take up and process antigen. Said dendritic cells are able to induce an anti-tumor response subsequent to administration to a cancer patient.

Applicant strongly disagrees with the allegations and assertions of the Examiner, but to further expedite prosecution claim 1 upon which claims 6 through 9 ultimately depend has been amended to recite "[a] method for producing an anti-tumor immune response comprising administration to an individual with a cancerous tumor a cell population comprising partially matured dendritic cells that have been partially matured *in vitro*, wherein the partially matured dendritic cells take up and process antigen *in vivo* and are enabled to induce an anti-tumor immune response subsequent to administration to the individual". Such amendment is believed to point out with greater particularity the method comprises administering an individual partially mature dendritic cells that have been induced to mature *in vitro* and that contact with antigen occurs *in vivo* subsequent to administration. Labeur *et al.* do not disclose or suggest such a method. Further, Bosch *et al.* and/or Chakraborty *et al.* do not disclose or suggest any element missing from the teachings of Labeur *et al.* to render obvious any of claims 1 and 6-9. Even if either Bosch *et al.* and/or Chakrabory *et al.* were to teach or suggest those elements alleged by the Examiner above, any combination of those references with Labeur *et al.* would not result in the present invention. If the references were combined as suggested by the Examiner, at most, the skilled artisan might use a maturation agent suggested by Bosch *et al.* to mature DCs that had been exposed to antigen prior to administration to a subject. That is not the invention as recited in any of claims 6 through 9. The addition of Chakrabory *et al.* which is alleged by the Examiner to teach the secretion of IL-12 by certain dendritic cells provides nothing that would disclose or suggest the present invention. As such, Labeur *et al.* when considered alone or in any combination with Bosch *et al.* and/or Chakrabory *et al.* do not disclose or suggest the invention as recited in claims 6 through 9.

Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 6 through 9 as being unpatentable over Labeur *et al.* in view of Bosch *et al.* and/or Chakrabory *et al.* in light of the amendments and remarks above.

Claims 13 through 18 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Labeur *et al.*, *J. Immunol.* 162:168-175, 1999 for reasons above. The Examiner has asserted that Applicant's prior response argues a limitation not in the claims. In particular, the Examiner has alleged that the claims do not limit that the administered, partially matured dendritic cells have not been exposed to tumor and that the ability to take up and process antigen by the dendritic cells is *in vivo*. The Examiner has further asserted that the dendritic cells taught by Labeur *et al.* certainly can take up and process antigen and that the dendritic cells are able to induce an anti-tumor response subsequent to administration to a cancer patient.

The Examiner has alleged that it would have been *prima facia* obvious for one of ordinary skill in the art at the time the invention was made to replace subcutaneous injection of the DCs taught by Labeur *et al.* with other common direct methods of administration, such as administration of DCs directly into the tumor, to a tissue area surrounding the tumor, into a lymph node directly draining a tumor area, directly to a circulatory vessel duct that delivers blood or lymph to the tumor or a tumor afflicted organ, or into the circulatory system such that the cells are delivered to the tumor or tumor afflicted organ because subcutaneous injection is not the optimal cell delivery system for *in vitro* generated DCs, at least in the mice, in view that DCs migrate very inefficiently into the regional lymph nodes after subcutaneous injection into mice, as taught by Labeur *et al.*

Applicant disagrees with the allegations and assertions of the Examiner, but to further expedite prosecution as set forth above claim 1 upon which claims 13 through 18 depend has been amended to recite "[a] method for producing an anti-tumor immune response comprising administration to an individual with a cancerous tumor a cell population comprising partially matured dendritic cells that have been partially matured *in vitro*, wherein the partially

matured dendritic cells take up and process antigen *in vivo* and are enabled to induce an anti-tumor immune response subsequent to administration to the individual". Such amendment is believed to point out with greater particularity the method comprises administering an individual partially mature dendritic cells that have been induced to mature *in vitro* and that contact with antigen occurs *in vivo* subsequent to administration. Labeur *et al.* do not disclose or suggest such a method. Further, contrary to the Examiners assertions, it would not have been obvious to one of ordinary skill to choose direct administration of the presently claimed DCs over subcutaneous injection. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 19 and 20 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Labeur *et al.*, *J. Immunol.* 162:168-175, 1999 (*supra*), in view of Nikitina *et al.*, 2001, *Int. J. Cancer* 94:825-833, 2001, for reasons already of record in paper of October 18, 2007. Specifically, the Examiner has asserted that Applicant's prior response argues a limitation not in the claims. The Examiner has asserted that the claims do not limit that the administered, partially matured dendritic cells have not been exposed to tumor and that the ability to take up and process antigen by the dendritic cells is *in vivo*. The Examiner has alleged that the dendritic cells taught by Labeur *et al.* certainly can take up and process antigen and that the dendritic cells are able to induce an anti-tumor response subsequent to administration to a cancer patient.

As such, the Examiner has alleged that it would have been *prima facia* obvious for one of ordinary skill in the art at the time the invention was made to combine DCs administration as taught by Labeur *et al.* with radiation therapy, because gamma irradiation induces the dramatic ability of DCs injected intravenous or subcutaneous to migrate and penetrate cancer tissue, and to take up apoptotic bodies, resulting in enhanced, potent antitumor response, as taught by Nikitina *et al.*

Applicant disagrees with the allegations and assertions of the Examiner. As set forth above, Labeur *et al.* does not teach the methods of the presently claimed invention. In particular, the DCs taught in Labeur *et al.* are exposed to antigen *in vitro* prior to administration

to an individual and are not the same as the DCs used in the presently claimed invention. Thus, Applicant submits that Labeur *et al.* even if combined with Nikitina *et al.* fail to teach or suggest each and every element of claims 19 and 20. Although Applicant does not believe that Labeur *et al.* teaches the method of the present invention recited in the pending claim, but to further expedite prosecution, claim 1 upon which claims 19 and 20 depend has been amended to recite "[a] method for producing an anti-tumor immune response comprising administration to an individual with a cancerous tumor a cell population comprising partially matured dendritic cells that have been partially matured *in vitro*, wherein the partially matured dendritic cells take up and process antigen *in vivo* and are enabled to induce an anti-tumor immune response subsequent to administration to the individual". Such amendment is believed to point out with greater particularity the claimed method comprises administering an individual partially mature dendritic cells that have been induced to mature *in vitro* and that contact with antigen occurs *in vivo* subsequent to administration. Labeur *et al.* do not disclose or suggest such a method. Further, contrary to the Examiners assertions, if the DCs of Labeur *et al.* were combined with the methods of Nikitina *et al.* the dendritic cells would be exposed to a tumor antigen *in vitro* prior to administration to a patient that had received radiation therapy. This is not the invention of claims 19 and 20. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 21 through 23, and 27 through 32 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, *Cancer* 89:2646-2654, 2000, in view of Sukhatme *et al.* (US 6,797,488), and as evidenced by Labeur *et al.*, *J. Immunol.* 162:168-175, 1999, or in the alternative, over Labeur *et al.*, *J. Immunol.* 162:168-175, 1999, in view of US 20050059151 (Bosch *et al.*, *supra*), and Chakraborty *et al.*, *Clin. Immunol.*, 94:88-98, 2000), as applied to claims 6 through 9 above, and further in view of Sukhatme *et al.* (US 6,797,488), for reasons already of record in paper of October 18, 2007.

The Examiner has summarize the prior response of Applicant as asserting that the DCs taught by Triozzi *et al.* are immature dendritic cells and are not partially matured dendritic

cells. In addition, the Examiner has alleged that the response asserts that Sukhatme *et al.* teach a pharmaceutical composition, and do not teach or suggest the claimed invention.

The prior response has been considered by the Examiner, but has not been found to be persuasive for the following reasons:

The DCs taught by Triozzi *et al.* which are exposed to GM-CSF and IL-4, have the same property as the claimed DCs, *i.e.*, having upregulated CD80, CD86, as taught by Triozzi *et al.*, and exhibit an intermediate maturation stage, as evidenced by Labeur *et al.* Labeur *et al.* teach that DCs cultured in the presence of GM-CSF only are immature (p.169, first column, first paragraph). Labeur *et al.* teach that DCs cultured in the presence of GM-CSF and IL-4 with or without the addition of F1t3L or TNF-alpha, exhibit an intermediate maturation stage (p. 169, first column, second paragraph). An intermediate maturation stage is reasonably interpreted as partially matured. Labeur *et al.* further teach that DCs generated from GM-CSF and IL-4, with or without the addition of TNF-alpha, exhibit intermediate ability to present antigen, after being exposed to the antigen (p.8, last paragraph, bridging p.9 and figure 3), which is the same as the claimed ability to uptake and process antigen.

The Examiner further believes that although the Triozzi reference does not explicitly teach that the generated DCs are partially mature, and retain the ability to uptake and process antigen, the claimed DCs appear to be the same as the prior art DCs, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). As such, the Examiner has asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the DCs

taught by Triozzi *et al.* with a pharmaceutically acceptable carrier, as taught by Sukhatme *et al.* for their storage.

Further, the Examiner has summarized Applicant's prior response as asserting that the DCs taught by Labeur *et al.* are contacted with tumor antigen prior to administration. In addition, the Examiner has alleged that Applicant's prior response asserts that one would not have expected that non-terminally mature DCs exhibit up-regulated CD80 and CD86. In addition, the Examiner has alleged that the prior response asserts that Labuer *et al.* cannot be combined with Bosch *et al.* and Chakraborty *et al.* and that Chakraborty *et al.* teaches DCs that are mature. As such, the Examiner has not found the response to be persuasive for the following reasons:

a) the Examiner believes that the response argues a limitation not in the claims;

b) the DCs taught by the combined art have the same property as the claimed DCs, because: 1) the DCs produced by a combination of only GM-CSF and IL-4 produce IL-12, and not IL-10, as taught by Chakraborty *et al.* (Table 1 on page 90),

2) up-regulation of CD80 and CD86 are property of DCs that produce IL-12, as taught by Chakraborty *et al.*, and

3) DCs cultured in the presence of GM-CSF and IL-4, with or without the addition of F1t3L or TNF-alpha, exhibit an intermediate maturation stage as taught by Labeur *et al.* (p.169, first column, second paragraph).

Applicant must again disagree with the rejection of the Examiner. First, Applicant believes that the claims clearly set forth that the dendritic cells administered, or formulated with a pharmaceutically acceptable carrier are partially matured. As such, all arguments related to Labeur *et al.* as disclosing a different dendritic cell for administration relate to a limitation recited in the claims. In spite of this belief, Applicant has amended claim 21 to read "[a] composition comprising partially mature dendritic cells combined with a

pharmaceutically acceptable carrier for *in vivo* administration, wherein the partially mature dendritic cells have been contacted *in vitro* with a dendritic cell maturation agent. The amendment is believed to point out with greater particularity that the dendritic cells are distinct from immature dendritic cells and mature dendritic cells, and that the partially mature dendritic cells have not been contacted with antigen.

Second, the dendritic cells of the present invention are not the same as those of the present invention. In particular, the dendritic cells of Triozzi *et al.* are immature dendritic cells and are not partially matured dendritic cells as set forth in claims 21-23 and 27-32. As set forth in the specification at page 9, line 28 through page 10, line 7 and page 11, lines 5 through 30, immature dendritic cells and partially mature dendritic cells differ in a number of ways including the levels of expression of a number of cell surface antigens, CD14, CD11c, CD80 and CD86, and in the phosphorylation level of a number of intracellular proteins including for example, jak2. The Examiner has asserted that the dendritic cells taught by the combined art have the same property as the claimed dendritic cells, because: 1) the dendritic cells produced by a combination of only GM-CSF and IL-4 produce IL-12, and not IL-10, as taught by Chakraborty *et al.* (Table 1 on page 90), and 2) up-regulation of CD80 and CD86 are property of dendritic cells that produce IL-12, as taught by Chakraborty *et al.* Applicant has reviewed Table 1 of Chakrabory *et al.* and contrary to the assertion of the Examiner found that the authors disclose that monocytic dendritic cell precursors cultured in the presence of GM-CSF and IL-4 can produce IL-10 and/or IL-12. Further, the authors disclose that up-regulation of CD80 and CD86, to at least some level as compared with monocytes, is a characteristic of immature dendritic cells. Applicant respectfully directs the Examiner to additional differences in the cell surface phenotype and the levels of IL-10 and/or IL-12 produce by monocytic dendritic cell precursors cultured in the present of GM-CSF and IL-4 and those cultured in the presence of GM-CSF, IL-4 and a dendritic cell maturation agent. Immature dendritic cells induced to mature by the addition of, in this example, IFNγ and SAC are clearly different in the amounts of IL-10 and/or IL-12 produced and in cell surface phenotype. As such, it is clear that the "partially mature" dendritic cells, immature dendritic cells contacted with a dendritic cell maturation agent,

as recited in the present claims do not have the same properties as the dendritic cells of either Labeur *et al.* or Triozzi *et al.* Applicant also again respectfully directs the Examiner to page 2652, right column, lines 2 through 11 of Triozzi *et al.* where the authors conclude that the immature dendritic cells administered *in vivo* lost the co-stimulatory molecule B7-2 (CD86A) and showed a decrease in the intensity of CD11c suggesting the possibility that immunostimulatory activity typical of dendritic cells was down regulated. Applicant discloses in the specification as filed that the "partially matured" dendritic cells, as claimed, down regulate cytokine receptors on the surface as compared with "immature" dendritic cells making them less sensitive or responsive to any immunosuppressive effects of cytokines in the intratumoral space. Immature dendritic cells as defined in the specification include monocytic dendritic cells cultured in the presence of GM-CSF and IL-4. As such, the "partially matured" dendritic cells of claims 21 through 23 and 27 through 32 are not the same as those taught by Triozzi *et al.* Sukhatme *et al.* is cited by the Examiner as disclosing a pharmaceutical carrier. As Triozzi *et al.* and Labeur *et al.* do not teach the "partially mature" dendritic cells of the present invention or methods for their administration, the addition of the teachings of Sukhatme *et al.* does not disclose of suggest the present invention.

The Examiner has also asserted that alternatively, with regards to claims 21-23 and 27-32, the teachings of Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* as set forth above when combined with the teachings of a pharmaceutically acceptable carrier render obvious the invention. According to the Examiner, one would have expected that the non-terminally matured dendritic cells taught by the combined art would up-regulate the co-stimulatory molecules CD80 and CD86, because one would have expected that the dendritic cells are those that secrete IL-12, and because up-regulation CD80 and CD86 is the property of dendritic cells that secrete IL-12, as taught by Chakraborty *et al.* The Examiner further alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the dendritic cellss taught by Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* with a pharmaceutically acceptable carrier, as taught by Sukhatme *et al.* for their storage.

Applicant again respectfully disagrees with the rejection of claims 21-23 and 27-32 as set forth by the Examiner. In particular, as set forth above, Labeur *et al.* does not teach the dendritic cells of the present invention. The dendritic cells taught in Labeur *et al.* are contacted with tumor antigen prior to administration. Thus, Applicant submits that Labeur *et al*. cannot be combined with Bosch *et al.* and Chakraborty *et al.* to teach or suggest the invention as set forth in claims 21-23 and 27-32. In addition, Applicant respectfully submits that contrary to the Examiner's assertions one of ordinary skill would not have expected "partially matured" dendritic cells to up-regulate CD80 and CD86 because they secrete IL-12. For example, Chakraborty *et al.* teach that culturing plastic-adherent circulating monocytes in GM-CSF and IL-4 followed by further maturation in interferon-gamma plus bacterial superantigens can give rise to two diametrically opposite types of DCs - one stimulatory and another inhibitory. See page 88, col. 1. Only the stimulatory cells were shown to synthesize IL-12 and expression of higher amounts of costimulatory molecules. The inhibitory dendritic cells synthesized IL-10. Moreover, the dendritic cells taught by Chakraborty *et al.* are mature and not "partially matured" dendritic cells as alleged by the Examiner. There is no disclosure or suggestion in Chakraborty *et al.* to administer or formulate as a pharmaceutical composition "partially mature" dendritic cells that have not been exposed to antigen. As such, for the reasons set forth above, one of ordinary in the art at the time of invention could not have nor would have been motivated to combine the references as suggested by the Examiner. Accordingly, Applicant respectfully requests that the rejection of claims 21-23 and 27-32 under 35 U.S.C. § 103(a) be withdrawn.

Claim 24 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, *Cancer* 89:2646-2654, 2000 (*supra*) in view of Sukhatme *et al.* (US 6,797,488; *supra*), and as evidenced by Labeur *et al.*, 1999, *J. Immunol.* 152:168-175, 1999 (*supra*) as applied for claim 21, and further in view of Murphy *et al.* (US 5,788,963, *supra*), or in the alternative, over Labeur *et al.*, *J. Immunol.* 162:168-175, 1999 (*supra*) in view of US 20050059151 (Bosch *et al.*), and Chakraborty *et al.*, *Clin. Immunol.* 94:88-98, 2000, *supra*), as applied to claim 21, and further in view of Murphy *et al.* (US 5,788,963), for reasons already of record.

The Examiner has summarized Applicant's prior response as asserting that the DCs taught by Triozzi *et al.* are immature dendritic cells and are not partially matured dendritic cells. In addition, the Examiner has alleged that the prior response asserts that Sukhatme *et al.* teach a pharmaceutical composition, and do not teach or suggest the claimed invention. The Examiner also alleges that the prior response asserts that Murphy *et al.* teach cryopreservation and thus do not teach or suggest each element of the claimed composition.

The prior response has been considered by the Examiner but not found to be persuasive for the following reasons:

The DCs taught by Triozzi *et al.* which are exposed to GM-CSF and IL-4, has the same property as the claimed DCs, *i.e.*, having upregulated CD80, CD86, as taught by Triozzi *et al.* and exhibit an intermediate maturation stage, as evidenced by Labeur *et at. supra.* As such, the Examiner has asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to cryopreserve the generated DCs taught by Triozzi *et al.*, Sukhatme *et al.*, and Labeur *et al.*, using the method taught by Murphy *et al.* for extended use of the generated DCs.

Still further, the Examiner has summarized Applicants' prior response as asserting that Labeur *et al.* do not teach the partially mature DCs of the claimed invention and that a combination of Labeur *et al.*, Bosch *et al.*, Chakraborty *et al.*, and Murphy *et al.* fail to teach or suggest each and every element of claim 24. The Examiner has not found this argument to be persuasive for the following reasons:

In addition, the Examiner believes that the DCs taught by the combination of Labeur *et al.*, Bosch *et al.*, Chakraborty *et al.* have the same properties as the claimed DCs as set forth above. As such, the Examiner believes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to cryopreserve the generated DCs taught by Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* using the method taught by Murphy *et al.* for extended use of the generated DCs.

Applicant respectfully disagree with the rejection of claim 24 as set forth the Examiner. As above regarding claim 21, the dendritic cells taught by Triozzi *et al.* are immature dendritic cells and are not the same as the partially mature dendritic cells of the present invention. Chakrobory *et al.* clearly show that there are phenotypic differences between monocytic dendritic cell precursors cultured in the presence of GM-CSF and IL-4 and monocytic dendritic cell precursors cultured in the presence of GM-CSF, IL-4, and a dendritic cell maturation agent. In addition, Labeur *et al.* does not disclose the same method or composition as Triozzi *et al.* and can not be used in any combination to characterize the dendritic cells of Triozzi *et al.* as being in an intermediate stage. Labeur *et al.* discloses methods for the differentiation and maturation of murine bone marrow dendritic cell precursors to mature dendritic cells. It is well known in the art that the cytokines and methods used for the differentiation and maturation of murine bone marrow dendritic cell precursors are not the same as for monocytic dendritic cell precursors. Further, as set forth above, the combination of Sukhatme *et al.* does not suggest or disclose the composition of claim 21. Therefore, any combination of Triozzi *et al.*, Sukhatme *et al.*, in view of Labeur *et al.* with Murphy *et al.*, alleged to teach cryopreservation of dendritic cells, do not teach or suggest each and every element of dependent claim 24.

Alternatively, with regards to claim 24, the Examiner notes that the teaching of Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* has been set forth above and that the references do not teach cryopreservation of the DCs subsequent to their partial maturation, *i.e.*, after their generation. As above, the Examiner alleges that Murphy *et al.* teach cryopreservation of DCs. According to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to cryopreserve the generated DCs taught by Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* using the method taught by Murphy *et al.* for extended use of the generated DCs.

Applicant respectfully disagrees with the rejection of claim 24 as set forth by the Examiner. As set forth above, Labeur *et al.* does not teach or disclose the partially matured dendritic cells of the presently claimed invention. Also as set forth above, Chakraborty *et al.* teaches that monocytic dendritic cell precursors cultured in GM-CSF and IL-4 have a very

different phenotype than the same cells cultured in the presence of GM-CSF, IL-4 and a dendritic cell maturation agent. Thus, Applicant submits that Labeur *et al.* even if combined with Bosch *et al.*, Chakraborty *et al.*, and Murphy *et al.* fail to teach or suggest each and every element of claim 24. As such, the Examiner is requested to reconsider and withdraw the rejection of claim 24 under 35 U.S.C. § 103(a).

Claims 25-26 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, *Cancer* 89:2646-2654, 2004 (*supra*) in view of Sukhatme et al. (US 6,797,488; *supra*), and as evidenced by Labeur *et al.*, *J. Immunol.* 162:168-175, 1999 (*supra*) as applied for claim 21, and further in view of Murphy *et al.* (US 5,788,963, *supra*), or in the alternative, over Labeur *et al.*, *J. Immunol.* 162:168-175, 1999 (*supra*) in view of US 20050059151 (Bosch *et al.*, *supra*), and Chakraborty *et al.*, *Clin. Immunol.* 94:88-98, 2000, *supra*), as applied to claim 21, and further in view of Murphy *et al.* (US 5,788,963, *supra*) for reasons already of record. In particular, the Examiner alleges that the dendritic cells taught by the combination of Triozzi *et al.*, Sukhatme *et al.*, and Labeur *et al.* have the same properties as the claimed dendritic cells, as set forth above. Further, the Examiner believes that it would have been obvious that the dendritic cells taught by Triozzi *et al.*, Sukhatme *et al.*, and Labeur *et al.* have been isolated from the individual to be treated, as suggested by Murphy *et al.* to avoid unwanted rejection of foreign dendritic cells. In addition, the Examiner believes that it would have been obvious that the dendritic cells taught by Triozzi *et al.*, Sukhatme *et al.*, and Labeur *et al.* have been isolated from a healthy individual, and HLA-matched to the individual to be treated as taught by Murphy *et al.* to increase the number of available dendritic cells, for example, in situations where the patient to be treated cannot provide sufficient dendritic cells, as taught by Murphy *et al.* Still further, the Examiner has alleged that an HLA-matched dendritic cells would be necessary, because antigen presentation of dendritic cells is restricted to the complementing HLA molecule, in view of the teaching of Murphy *et al.*

Applicants' prior response has been summarized by the Examiner as asserting that a combination of Labeur *et al.*, Bosch *et al.*, Chakraborty *et al.*, and Murphy *et al.* fail to teach or

suggest each and every element of claims 25 and 26. The response has been considered by the Examiner but has not found to be persuasive for the following reasons:

The dendritic cells taught by the combination of Labeur *et al.*, Bosch *et al.*, Chakraborty *et al.* have the same properties as the claimed dendritic cells, as set forth above. As such, the Examiner believes that it would have been obvious that the dendritic cells taught by Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* have been isolated from the individual to be treated, as suggested by Murphy *et al.* to avoid unwanted rejection of foreign dendritic cells. In addition, the Examiner believes it would have been obvious that the dendritic cells taught by Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* have been isolated from a healthy individual HLA-matched to the individual to be treated as taught by Murphy *et al.* to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy *et al.* Further, the Examiner has asserted that an HLA-matched DCs would be necessary, because antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy *et al.*

Applicant respectfully disagrees with the rejection of claims 25 and 26 as set forth by the Examiner. As set forth above regarding claim 21, the dendritic cells taught by Triozzi *et al.* are not partially matured dendritic cells as recited in the present claims. Further, the teachings of Labeur *et al.* as applied by the Examiner to Triozzi *et al.* compares culture conditions and resulting phenotypes of different cells. In Labeur *et al.* bone marrow dendritic cell precursors and cultured to form mature dendritic cells or an "intermediate stage" dendritic cells. While Triozzi *et al.* is directed to the administration of immature dendritic cells produced from the differentiation of monocytic dendritic cell precursors. It is well known to the skilled artisan that the methods for differentiation and maturation of dendritic cells from murine bone marrow derived dendritic cell precursors are different from those for monocytic dendritic cell precursors. As such, the teachings of Labeur *et al.* are not relevant to characteristics of the cells used by Triozzi *et al.* Moreover, for reasons mentioned above, Triozzi *et al.*, Labeur *et al.*, Sukhatme *et al.* and Murphy *et al.* whether considered alone or in any combination fail to teach or suggest either independent claim 21 or its dependent claims, for example, claims 25 and 26.

Alternatively, the Examiner has rejected claims 25 and 26 noting that the teachings of Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* as set forth above do not teach that the generated dendritic cells can be isolated from the individual to be treated or from a healthy individual HLA-matched to the individual to be treated. But, the Examiner alleges that Murphy *et al.* teach that dendritic cells can be obtained from a prostate cancer patient to be treated, or from a healthy individual with matched HLA in terms of HLA antigens, because patients previously treated radiation or chemotherapy often are not able to provide sufficient or efficient dendritic cells. The Examiner also asserts that Murphy *et al.* teach that $CD8^+$ T cells, after interaction with antigen presenting cells, which express MHC class I or II molecule associated with the antigen, are sensitized and capable of killing any cells that express the specific antigen associated with matching MHC class I molecule. The Examiner has also noted that dendritic cells are antigen presenting cells.

According to the Examiner, it would have been obvious that the dendritic cells taught by Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* can be isolated from the individual to be treated, as suggested by Murphy *et al.* to avoid unwanted rejection of foreign dendritic cells. The Examiner further alleges that it would have been obvious that the dendritic cells taught by Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* can be isolated from a healthy individual HLA-matched to the individual to be treated as taught by Murphy *et al.* to increase the number of available dendritic cells, for example, in situations where the patient to be treated cannot provide sufficient dendritic cells, as taught by Murphy *et al.* Still further, the Examiner alleges that HLA-matched dendritic cells would be necessary, because antigen presentation of dendritic cells is restricted to the complementing HLA molecule, in view of the teaching of Murphy *et al.*

Applicant respectfully disagrees with the rejections and do not acquiesce to any reasoning provided by the Examiner. As set forth above, Labeur *et al.* does not teach the partially mature dendritic cells of the presently claimed invention. Also, as set forth above Chakrabory *et al.* teaches that monocytic dendritic cell precursors cultured in the presence of GM-CSF and IL-4 are phenotypically distinct from monocytic dendritic cell precursors cultured in the presence of GM-CSF, IL-4 and a dendritic cell maturation agent. In addition, Labeur *et al.*

teaches method and characteristics of immature and mature dendritic cells produced from bone marrow dendritic cell precursors. Any characteristics defining the cells produced by the method can not be extrapolated to immature or mature dendritic cells produced by the same methods from monocytic dendritic cell precursors. It is well known to the skilled artisan that the methods for differentiation and maturation of dendritic cells from murine bone marrow are different from those for dendritic cells produced from human monocytic dendritic cell precursors. Thus, Applicant submits that any combination of Labeur *et al.* with Bosch *et al.*, Chakraborty *et al.*, and Murphy *et al.* can not teach or suggest the invention as set forth in claims 25 and 26. In view of the above remarks Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 25 and 26 under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 17 December 2008

By: _____
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